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EXAMINER	
GODDARD, LAURA B	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,515	PASTAN ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008 and 18 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,7-39 and 41-55* is/are pending in the application.

4a) Of the above claim(s) *12-23,31-38 and 41-46* is/are withdrawn from consideration.

5)☒ Claim(s) *1,5,7-11,39 and 48* is/are allowed.

6)☒ Claim(s) *24-30* is/are rejected.

7)☒ Claim(s) *4,47 and 49-55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submissions filed on April 30, 2008 and July 18, 2008 have been entered.

Claims 1, 4, 5, 7-39, and 41-55 are pending. Claims 54 and 55 are new. Claims 1, 4, 10, 11, 17, 24, 39, 41, 43, and 51-53 are amended. Claims 12-23, 31-38, and 41-46 remain withdrawn. Claims 1, 4, 5, 7-11, 24-30, 39, and 47-55 are currently being examined.

Claim Objections

2. Claim 4 is objected to because of the following informalities: It appears there is a grammatical typo. The claim recites "comprising at the least eight consecutive amino acids" when it appears it should recite "comprising the at least eight consecutive amino acids" for appropriate antecedent basis based on the "(1) at least eight consecutive amino acids" recited in claim 1. Appropriate correction is required.

3. Claims 54 and 55 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 54 is dependent on claim 1. Claim 1 recites (1) a polypeptide comprising at least eight consecutive amino acids of amino acids 157-933 of SEQ ID NO:1, wherein the polypeptide must be eight to ten amino acids in length and bind a MHC. Claim 1 also recites (2) a polypeptide comprising SEQ ID NO:1. Claim 54 is dependent on claim 1 but recites a polypeptide consisting of amino acids 157-933 of SEQ ID NO:1 which is neither eight to ten amino acids long nor comprises SEQ ID NO:1 as required by claim 1 and is outside the scope of claim 1 polypeptides. Claim 55 is dependent on claim 54 and encompasses polypeptides consisting of one of SEQ ID NOs:3-10, however, these polypeptides are outside the scope of claim 54 because they do not consist of amino acids 157-933 of SEQ ID NO:1 as required by claim 54.

4. Claim 47 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 4. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 49-53 are objected to for being dependent on objected claim 47.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method for detecting prostate tissue in a subject comprising detecting expression of the polynucleotide of claim 7 in a sample from the subject, wherein detection of expression of the polynucleotide indicates the presence of prostate tissue**, does not reasonably provide enablement for detecting prostate cancer or using any control for comparison. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are now drawn to a method for detecting prostate cancer or prostate tissue in a subject, comprising detecting expression of the polynucleotide of claim 7 in a sample from the subject, wherein an increase in the expression of the polynucleotide as compared to a control indicates the presence of the prostate cancer or the prostate tissue (claim 24), wherein detecting the expression of the polynucleotide comprises detecting mRNA in a Northern Blot analysis, an RNA Dot blot, or an RT-PCR assay (claim 25).

The specification discloses SV-NGEP sequence SEQ ID NO:2 which was detected as a gene uniquely expressed in normal prostate tissue (Fig. 3; Examples 2 and 3). The specification discloses that SEQ ID NO:2 is also expressed in prostate cancer samples (Example 5).

Bera et al (PNAS, 2004, 101:3059-3064) teach SEQ ID NO:2 as a long form splice variant of "Novel Gene Expressed in Prostate" (NGEP-L) which is expressed only in prostate tissue (p. 3061, col. 2). Bera et al teach that NGEP is expressed only in normal prostate and prostate cancer cells (p. 3063, col. 1). Das et al (poster presentation from the AACR meeting, 2007, Exhibit D) teach that SV-NGEP (NGEP-L) protein is detected in both normal prostate and prostate cancer.

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for detecting

prostate cancer in a subject, comprising detecting expression of SEQ ID NO:2. It is clear from the art and the instant specification that SEQ ID NO:2 is not differentially expressed between normal and cancerous prostate, therefore, one of skill in the art could not detect prostate cancer based on the expression of SEQ ID NO:2. The specification provides neither guidance on nor exemplification of how to correlate the presence of SEQ ID NO:2 with the presence of prostate cancer as distinguished from the presence of normal prostate. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and **specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome**. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and

subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Given the expression of SEQ ID NO:2 is not specific to prostate cancer and cannot distinguish between normal prostate and the presence of prostate cancer, one of skill in the art could not predictably detect prostate cancer based on the expression of SEQ ID NO:2.

Further, the specification does not provide guidance or examples for what control or standard would be indicative of prostate cancer or prostate tissue based on sample comparison. Given SEQ ID NO:2 expression is unique to prostate tissue in general, it is unclear what control would function to identify prostate tissue or prostate cancer as having any increased level of either mRNA or protein expression to predictably detect prostate tissue or cancer.

Therefore, in view of the state of the art, the quantity of experimentation necessary to distinguish between normal and prostate cancer, the lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Relevant Arguments

6. Applicants argue that the claims as amended do not require that prostate cancer be distinguished form normal prostate (p. 22).

The arguments have been considered but are not found persuasive because the claims still recite the detection of prostate cancer, as distinguished from prostate tissue, and the detection of prostate cancer, specifically, is not enabled for the reasons of record and as set forth above.

7. Claims 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for producing an immune response against a cell expressing a polypeptide of claim 1 in a subject, the method comprising administering to the subject a therapeutically effective amount of the polypeptide of claim 1, or a polynucleotide encoding the polypeptide, thereby producing the immune response (claim 26), the method of claim 26, wherein the immune response is a T cell response (claim 27), the method of claim 26, wherein the immune response is a B cell response (claim 28), the method of claim 26, wherein the subject has prostate cancer (claim 29), the method of claim 29, wherein the immune response decreases the growth of the prostate cancer (claim 30).

The specification discloses a predicted amino acid sequence for an SV-NGEP protein based on the nucleotide sequence of SEQ ID NO:2 (p 51, lines 18-21; Example 3). SEQ ID NO:2, the polynucleotide, was found to be uniquely expressed in prostate tissue and prostate cancer tissue but not in other normal tissues (Example 2). The specification does not disclose any working examples demonstrating protein expression of SV-NGEP SEQ ID NO:1 in prostate tissue or prostate cancer or the protein's role in immunotherapy. The specification prophetically asserts administering a SV-NGEP polypeptide to a subject suffering from a disease, such as prostate cancer, to generate an immune response to slow the proliferation of cells expressing SV-NGEP. The specification discloses that a "therapeutically effective amount" of SV-NGEP is that

which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer (p. 39). The specification contemplates administering a SV-NGEP polypeptide to induce a CTL response (p. 40; Example 9) and discloses the prediction of 9-mers of SEQ ID NO:1 that would bind to HLA2-01 (an MHC molecule) (p. 25, lines 12-26) but does not provide any working examples of generating any immune response, humoral or cellular, against SV-NGEP in a subject that would decrease the growth of prostate cancer or be therapeutic as claimed and contemplated.

The specification does not provide guidance or examples for treating prostate cancer comprising administering SV-NGEP polynucleotide or polypeptide or working examples of the claimed polypeptide or polynucleotide functioning therapeutically *in vivo*. Given SV-NGEP is a self-antigen and self-antigens are reasonably expected to be tolerated by the immune system, one of skill in the art could not predictably generate an immune response, humoral (B-cell, antibodies) or cellular (T-cell), sufficient to therapeutically treat a subject *in vivo* for a disease or prostate cancer as claimed and contemplated.

The art teaches the unpredictability of treating cancer using peptide-based vaccines to elicit a CTL response, particularly regarding self-antigens. Lee et al (J. Immunol., 1999, 163:6292-6300), specifically teach that although a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, this response does not associate with a clinically evident regression of metastatic melanoma (see abstract). Further, Kirkin et al (1998, APMIS,

106 : 665-679) teach that in particular for tumor antigens, for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Further, Chaux et al, (Int J Cancer, 1998, 77: 538-542) teach some of the CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which is different from the *in vitro* condition in which the synthetic peptides are in high number when incubated with the cells (p.541, second column, second paragraph). Given the above, even if a peptide on a cell line cell was recognized by T-cells *in vitro*, it could not be predicted that the T-cells would recognize these peptides *in vivo* and if not recognized *in vivo*, it is clear that one would not know how to use the SV-NGEP peptide or protein predictably as a therapeutic. In addition, as drawn to cancer vaccines, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence, as set forth above, suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches that even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

Celis (J of Clinical Investigation, 2002, 110:1765-1768) summarize the problems associated with peptide vaccine failure. Celis teaches that the advantages that peptide vaccines have to offer are diminished by their inherent lack of immunogenicity which so

far has been reflected by their not-so-spectacular results in the clinic. Vaccines consisting of peptides are likely to be ignored and will likely be ineffective at inducing T-cell immunity. Peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of rapid biodegradation (e.g., by proteases) or, worse, because of the induction of T-cell tolerance/anergy, which results from the antigenic stimulation of CTLs by nonprofessional APCs. An additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of CTLs that, while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize target cells that naturally process and present the peptide epitope, such as infected or malignant cells. Obviously, these "low-quality" CTLs would have little effect in fighting and controlling disease. One reason for generation of such low-quality CTLs by peptide vaccine is the induction of CTLs with low affinity for antigen, which will require a high density of specific peptide/MHC complexes on the target-cell surface to exert their effector function. *In vitro*, the induction of low-affinity CTLs usually results from the use of high concentrations of peptide, generating a high level of specific peptide/MHC complexes on APCs, which will effectively activate these CTLs. The prediction is that high densities of peptide/MHC complexes on APCs *in vivo* resulting from an excessive peptide dose will also produce low-quality CTLs with low affinity for the antigen. Finally, another cause for the induction of low-quality CTLs is the use of vaccines produced with synthetic peptides representing cryptic T cell epitopes, which are not expressed on the surface of the infected or tumor target cells. CTLs recognizing

cryptic epitopes will be unable to interact with infected or tumor target cells and will also be useless in disease control (p. 1765).

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as claimed or as contemplated with a reasonable expectation of success. Given the unpredictability that the SV-NGEP polypeptide of claim 1 would elicit an adequate T cell response *in vivo*, useful for the treatment of cancer as claimed and contemplated, the lack of adequate disclosure in the specification, the absence of enabling art, and in view of the complex nature of the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

With regards to administering a polynucleotide encoding the polypeptide of claim 1, the art recognizes that gene therapy is highly unpredictable. Rolland (Advanced Drug Delivery Reviews, 2005, 57:669-673), teach the limitations of gene therapy. Tissue distribution and persistence of expression plasmids is dependent on several parameters, including the route of administration, the formulation, and the use of a device. For instance, DNA can be detected in all major organs after intramuscular injection, with rapid clearance from all those tissues with the exception of the injection site. Intravenous (systemic) and intratumoral have shown a far more rapid elimination from the injected compartment, ranging from minutes to days. To date, there is a void of plasmid pharmacokinetic data in humans, thus making it impossible to evaluate the predictability of the animal models (p. 671, cols. 1 and 2). Rolland teach that DNA

plasmids have many barriers to overcome for efficient gene transfer and expression. Following passive or active distribution of plasmids to target tissues after *in vivo* administration and uptake by the cells, plasmids need to be able to navigate through the cell cytoplasm before reaching the nucleus where gene expression can be initiated. This intracellular trafficking of plasmids remains a poorly understood series of events, making the rational design of delivery elements to overcome those rate-limiting steps a major challenge. At the end of the DNA plasmid's journey from the site of administration to the nucleus of the transfected cell, the plasmid expression system needs to be functional and contain specific elements for gene expression to occur at the appropriate levels, with the tight specificity and accuracy, and for an adequate period of time (p. 672, col. 1). McCormick (Nature Reviews, 2001, 1:130-141) teaches the challenges of gene therapy including the need for a vector or virus delivering the nucleic acid to avoid neutralization by the immune system, the rapid clearance of systemically administered agents from the bloodstream by the liver, and if the agent survives that, the agent must leak from the blood vessels into tumors and spread within the heterogeneous mass of the tumor (p. 137, col. 2). McCormick teaches that although the biological principles of cancer gene therapy are sound, translating these principles into reality remains a formidable- perhaps prohibitive- challenge (p. 138, col. 2). The specification provides no working examples demonstrating induction of a therapeutic immune response by administering a polynucleotide encoding the polypeptide of claim 1 and given the art teaches the complexity and unpredictability of DNA therapy, compounded by the unpredictability in producing an immune response that is therapeutic, one of skill in the

art would be subject to a high quantity of experimentation to practice the invention as claimed.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

8. All other rejections recited in the Office Action mailed January 30, 2008 are hereby withdrawn in view of amendments and arguments.

9. **Conclusion:** Claims 1, 5, 7-9, 10, 11, 39, and 48 are allowed. Claims 4, 47, and 49-55 are objected to. Claims 24-30 are rejected.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Examiner, Art Unit 1642